REMARKS

The applicants thank the Examiner for consideration of applicants' arguments presented in the response submitted on February 18, 2007 to the prior office action of October 17, 2006 and withdrawal of the rejections stated in that office action. The applicants also thank the Examiner for the allowance of claims 27-31.

In the current office action, the Examiner rejected claims 6, 8, 9, 11-13, 15-17, 19 and 37-39 under 35 USC 112, first paragraph, claims 1, 2, 4 and 5 under 35 USC 102(b) and claims 1, 2, 4, 5, 32 and 34-39 under 35 USC 103(a). The Applicants have requested claims 6, 8, 9, 11-13, 15-17, 19 and 37-39 be amended.

The applicants believe no new matter is introduced as a result of such amendment.

Rejection Under 35 USC 112, First Paragraph

The Examiner rejected claims 6, 8, 9, 11-13, 15-17, 19 and 37-39 under 35 USC first paragraph for failing to comply with the enablement requirement. The applicants respectfully suggest that claims 6, 8, 9, 11-13, 15-17, 19 and 37-39 meet the requirements of 35 USC 112, first paragraph, with respect to the enablement standard. However, to facilitate the prosecution of the instant application, the applicants have requested claims 6, 8, 9, 11-13, 15-17, 19 and 37-39 be amended to delete the term "pharmaceutical." The applicants note that such a construction is already present in the claims (see for example, independent claim 1) and such construction has not been objected to.

Rejections Under 35 USC 102

The Examiner rejected claims 1, 2, 4 and 5 under 35 USC 102(a) as being anticipated by Carter et al. (Mol. and Cell. Biol., 1990, 10(12):6460-6471) (hereinafter Carter) as evidenced by Li et al (Nucleic Acids Research, 2003, 32(20):5848-5857) (hereinafter Li). In making this rejection, the Examiner states that the single chain antibody disclosed by Li and the present disclosure and mAb 18-2 disclosed by Carter each share the same CDRs (namely, the CDRs encoded by SEQ ID NOS: 18-23 of the instant specification). The Examiner further states that since the single chain antibody taught by Li binds SEQ ID NO: 16 and that since the mAB 18-2 taught by Carter and the single chain antibody taught by Li have identical CDRs and exhibit

identical binding to DNA-PKcs, then mAb 18-2 would bind to SEQ ID NO: 16, which is found outside of the catalytic region of DNA-PKcs. The Examiner also states that mAb 18-2 inhibits less than 50% of the enzymatic activity of DNA-PKcs and invited the applicants to provide evidence that the prior art composition does not perform the same function as the claimed composition.

As an initial matter, the applicants believe it is instructive to briefly review the state of the art regarding DNA-PK at the time of the Carter. Essentially, all Carter knew was that DNA-PK was activated by association with double-stranded DNA (Carter, last sentence of abstract and page 6460, column 2, first full paragraph) and that mAb 18-2 inhibited an enzyme activity by 50% (Carter et al., page 6464, column 1, first full paragraph). Carter did not appreciate the function and composition of DNA-PK. In fact, Carter did not definitively identify the enzyme to which the monoclonal antibody bound as being DNA-PK. On page 1469, Carter states "DNA-PK appears to be a novel type of protein kinase. If the 300 kDa polypeptide is indeed the enzyme...". Later on the same page, Carter states "We cannot at present rule out the possibility that DNA-PK is another protein that strongly associates with the 300kDa polypeptide and requires this association for its stability in vitro but is present in such small amounts that it is not easily detected by silver staining." While the monoclonal antibody taught by Carter was shown to bind to a protein that might have been DNA-PK, Carter did not teach or suggest the sequence bound by the mAb 18-2. In particular, there is no suggestion in Carter that binding of mAb 18-2 would result in inhibition of non-homologous end joining, that DNA-PK is related to non-homologous end joining or that DNA-PK associated with or bound to the free ends of double-stranded DNA. Indeed, Carter thought it unlikely that DNA-PK associated with or bound the free ends of double-stranded DNA (Carter paper, page 6469, column 2, last paragraph, continuing on to the top of the next page). In fact, binding of DNA-PK to the free ends of double-stranded DNA is essential for non-homologous end joining.

After Carter, it was determined that DNA-PK played a role in DNA repair through an association or binding of DNA-PK with the ends of double stranded DNA breaks, and that DNA repair could be inhibited by alteration of the catalytic region of DNA-PK to cause 100%

impairment of DNA-PK enzyme activity (so-called "kinase-dead DNA-PK"). This latter result is consistent with the mechanism of action for protein kinase inhibitor drugs such as, for example, gefitinib, which completely extinguishes the enzyme activity of EGFR protein kinase (Cohen et al, "United States Food and Drug Administration Drug Approval Summary: Gefitinib (ZD1839; Irressa) Tablets" Clinical Cancer Research 10:1212-1218, February 2004; section on Mechanism of Action.)

Given this state of knowledge, the two most obvious mechanisms for the single chain antibody of the present disclosure would be: (i) to completely (or at least largely) extinguish the DNA-PKcs enzyme activity, or (ii) to somehow prevent DNA-PKcs from associating or binding with double stranded DNA. However, the present disclosure demonstrates that neither mechanism explained the function of the single chain antibody of the present disclosure. Specifically, the present disclosure reports that the single chain antibody described does not block the interaction of DNA-PKcs with double stranded DNA and does not result in a total or near total inhibition of DNA-PKcs activity. Given the fact that approximately 50% of DNA-PKcs activity remained, the person of ordinary skill in the art would have believed that the continued binding of DNA-PK to double stranded DNA with 50% or more of retained enzyme activity would continue to catalyze a substantial amount of non-homologous end joining. The surprising, near-complete inhibition of non-homologous end joining by the single chain antibody of the present disclosure is an unexpected and counter-intuitive result and is due to a mechanism that was not reported or suggested by previous inhibitors of DNA-PKcs that inhibited DNA repair or by Carter. This uncertainty as to the mechanism of action of the single chain antibody of the present disclosure is echoed in Li (Li et al., page 5855, column 1, last sentence of second full paragraph).

The assertions of Carter as discussed above teach away from the disclosure of the present application as set forth in claims 1, 2, 4 and 5, which claim a composition (claims 1, 2 and 4) or single chain antibody (claim 5) that binds to DNA-PKcs and inhibits non-homologous end joining. Again, nothing in the Carter et al. reference teaches or suggests that mAb 18-2 inhibits in any way non-homologous end joining. Therefore, the Carter et al. reference does not teach or

suggest the disclosed single chain antibody as disclosed by the applicants or that the single chain antibody as disclosed by applicants (or any other antibody for that matter) inhibits non-homologous end joining.

The 102(b) Rejection

The present specification states that the inhibition of non-homologous end joining as disclosed results from steric inhibition caused by the binding of the disclosed single chain antibody to DNA-PKcs. As discussed above, the prior art did not teach or suggest this mechanism of action for the single chain antibody or mAb 18-2. The applicants respectfully suggest that the ability of the single chain antibody of the present disclosure to inhibit non-homologous end-joining is not anticipated by the Carter reference when taken in light of Li.

In making the anticipation rejection, the Examiner uses the following logic: because the single chain antibody taught by Li and the present disclosure binds the sequence of SEQ ID NO. 16, the monoclonal antibody mAb 18-2 taught by Carter would necessarily also bind SEQ ID NO. 16, as evidenced by (i) the single chain antibody of Li and the present disclosure and mAb 18-2 sharing the same CDRs; (ii) the single chain antibody of Li and the present disclosure and mAb 18-2 each demonstrating identical binding to DNA-PKcs; and (iii) the single chain antibody of Li and the present disclosure and mAb 18-2 each inhibiting the kinase activity of DNA-PKcs less than about 50% (although Carter failed to identify the actual target of mAb 18-2 activity). The applicants respectfully disagree with the Examiner's conclusions.

<u>The single chain antibody of the present disclosure and mAb 18-2 display different binding characteristics</u>

Regarding the Examiner's assertions that the binding of mAb 18-2 and the single chain antibody of Li and the present disclosure are identical, the applicants respectfully point out that the binding of mAb 18-2 and the single chain antibody to DNA-PKcs has not been proven to be identical. As can be seen in an inspection of FIG. 1C from Li and the present disclosure, mAb 18-2 and the single chain antibody of the present disclosure each bind to DNA-PKcs. However, there is no data to show that the sequences bound are identical. Examination of FIG. 1C from Li and the present disclosure show different binding patterns in the immunoblot experiment

illustrated therein. Therefore, mAb 18-2 and the single chain antibody of and the present disclosure show empirical differences in the binding to DNA-PKcs under the same experimental conditions.

Furthermore, the binding characteristics of the single chain antibody of the present disclosure could not be predicted from Carter. The results in Carter were obtained using purified cellular extracts in an extra-cellular environment. However, the present disclosure employs experiments conducted in an intra-cellular environment using a variety of cell lines. Examples 3-9 of the present disclosure provide whole cell based experiments that demonstrate the effectiveness of the disclosed single chain antibody in inhibiting DNA repair and non-homologous end joining in an intracellular environment. The results of extra-cellular experiments using purified components are not predictive of the results to be obtained using model cell systems as shown by the applicants. As the Examiner has pointed out on pages 3-5 of the instant office action, the biotechnology art is unpredictable and results from different experimental conditions cannot be easily extrapolated from one condition to the other. Therefore, there is no teaching or suggestion that mAb 18-2 as disclosed by Carter would display similar binding characteristics to the single chain antibody of the present disclosure in an actual intracellular environment.

Derivation of a single chain antibody from a parental monoclonal antibody does not imply similar function or binding characteristics

It is widely recognized that the art of transforming a monoclonal antibody to a single chain antibody is a complex process that is not completely understood. Success of such a transformation cannot be guaranteed. The Examiner cites Bejcek for the proposition that it would have been obvious for one of ordinary skill in the art to take the monoclonal antibody as taught by Carter and create the single chain antibody as taught by the present disclosure such that the single chain antibody would have the same functional and binding characteristics as the parental monoclonal antibody. Bejcek disclosed methods for the production of single chain antibodies from monoclonal antibodies and further disclosed the advantages of producing such

single chain antibodies. Specifically, the Bejcek reference teaches the production of three single chain antibodies to the CD19 antigen.

However, the Bejcek paper explicitly states having possession of a monoclonal antibody does not translate into having a single chain antibody that binds the same target and performs the same function as the original monoclonal antibody. In the introduction, Bejcek states that "One problem with the production of antibody binding domains in this manner is that high affinity antibody binding cannot be successfully reconstituted in all instances. The parameters that govern the ability of an antibody to yield an scFv that can bind its target are unknown, thus necessitating the direct cloning and analysis of the candidate antibody gene segments" (see page 2346, second paragraph). Furthermore, in the discussion section, Bejcek states that "Because the effects of primary amino acid sequence on protein folding are not well understood, there is no known a priori method for determining the ability of a particular antibody to function when produced in an scFv." Indeed, the results of the Bejcek paper bear this out. The single chain antibody designated FVS193 did not bind to its CD19 target. The failure rate of converting parental monoclonal antibodies into corresponding single chain antibodies was greater than 33% in the experiments reported by Bejcek for the CD19 antigen.

Several other scientific references also discuss the unpredictability of transforming monoclonal antibodies into single chain antibodies. For example, Lamberski et al. (Expression and purification of a single-chain variable fragment antibody derived from a polyol-responsive monoclonal antibody, Protein Expression and Purification, 47, pp82-92, 2006; copy attached as Appendix A) reported that while a single chain antibody could be produced from the parental monoclonal antibody NT73, the produced single chain antibody had significantly different binding characteristics. In particular, the single chain antibody displayed significantly different ELISA-elution profiles from the parental NT73 monoclonal antibody, releasing its antigen under a wider variety of conditions than the parental antibody (see p. 90, second column and FIG. 7). Furthermore, the single chain antibody had a decreased affinity for the antigen as compared to the parental monoclonal antibody NT73 (see p.91, first column). These differences were noted despite the fact both the parent monoclonal antibody and the transformed single chain antibody

were each demonstrated to bind the same target. Therefore, the binding characteristics of the parental monoclonal antibody and the single chain antibody were significantly different. Lamberski stated that "It should be noted that not all scFv antibodies necessarily retain the same binding properties as the intact monoclonal antibody." (see p.91, second column). Furthermore, Lamberski cited a study that examined the production of single chain antibodies from monoclonal antibodies, wherein the monoclonal antibodies were selected to bind their antigen under conditions which destabilized protein-protein interactions (such as DMSO, guanidine hydrochloride, high salt and extreme pH). While single chain antibodies were produced, the binding properties of the single chain antibodies were found to be significantly different when compared to the parental monoclonal antibodies. Lamberski stated that "This suggested that when converted to a scFv antibody, the types and three-dimensional orientation of hydrophobic and hydrogen bonding and ionic molecular interactions between antibody and antigen may change." (see p. 91, second column to p. 92 first column).

In addition, Bose et al. (in the study cited by Lamberski et al. above) found that a single chain antibody produced from a parental monoclonal antibody that bound anti-Hepatitis B also had significantly different binding characteristics, although each bound the same antigen under certain conditions (Bose et al., Characterization and molecular modeling of a highly stable anti-Hepatitis B surface antigen scFv, Molecular Immunology, 40, pp617-31, 2003; copy attached as Appendix B). Bose states that it is well known that truncation and mutations can be generated during production of single chain antibodies (see p 620, second column). Furthermore, Bose showed that the single chain antibody binding differed from the parental monoclonal antibody binding when carried out in urea (Fig. 4A), DMSO (Fig. 4B), NaCl (FIG. 5A), when pH was varied (FIG. 5B) and in guanidium hydrochloride (Fig. 6). Bose traced these differences in binding characteristics to mutations in the framework and CDR regions of the single chain antibody as compared to the parental monoclonal antibody (see p. 624-627). Bose concluded that the mutations in specific residues of the single chain antibody altered the character of the single chain antibody binding.

Thus, until a single chain antibody was produced and tested for the functional effects claimed in the current application, one of ordinary skill in the art could not have known that such an antibody could be produced or that once produced it would have the desired properties. The Bejcek reference, as supported by the other references discussed above, is simply an invitation to experiment in order to create a desired single chain antibody. Therefore, the assumption that a single chain antibody and the parent monoclonal antibody would inherently have the same binding characteristics and the same function is not supported by the references cited by the Examiner in the instant office action and the additional references cited by the applicants. As a result, the assumption that mAb 18-2 would have the same binding characteristics and function as the single chain antibody of the present disclosure is not supported.

Indeed, the present disclosure clearly shows functional differences between the single chain antibody of the present disclosure and mAb 18-2 with regard to inhibition of non-homologous end joining. As can be seen in FIG. 2A of the present disclosure, the single chain antibody disclosed by the applicants is significantly more effective in inhibiting non-homologous end joining than mAb 18-2. In FIG. 2A, the single chain antibody disclosed by applicants resulted in essentially complete inhibition of non-homologous end joining when the single chain antibody was used at a concentration of 1.3 μM. However, when mAb 18-2 was used in the same assay, at the same concentration (1.3 μM) and under the same experimental conditions, mAb 18-2 was significantly less effective in inhibiting non-homologous end joining. Furthermore, even at a concentration of 2.6 μM, mAb 18-2 was not as effective in inhibiting non-homologous end joining.

<u>The activities displayed by the single chain antibody of the present disclosure and mAb 18-2 are unrelated to inhibition of non-homologous end joining</u>

mAb 18-2 was disclosed by Carter as inhibiting an enzymatic activity believed to be associated with DNA-PK; the single chain antibody of the present disclosure was also reported to inhibit the enzymatic activity of DNA-PKcs. However, the inhibition of DNA-PK enzymatic activity is not related to the inhibition of non-homologous end joining as described in the present specification; the present specification shows that non-homologous end joining activity is

substantially completely inhibited while enzymatic activity is inhibited less than about 50%. The present application points out (as discussed above) that the observed effects of the single chain antibody of the present disclosure are due to steric inhibition of non-homologous end joining. Given this unanticipated mechanism of action, one of ordinary skill in the art would have no reason to believe that decreasing the size of the antibody (such as occurs in the transition from a monoclonal antibody to a single chain antibody) would result in a single chain antibody with the function described (near complete inhibition of non-homologous end joining). The surprising result that the single chain antibody of the present disclosure provided almost complete inhibition of non-homologous end joining is an unexpected result that was not taught or suggested by Carter; the applicants' work subsequent to Carter identified the function of the single chain antibody and its mechanism of action.

For all these reasons, the inference of mAb 18-2 binding and function by reference to the single chain antibody of the present disclosure is not supported. Indeed, as discussed above, the binding characteristics and function of mAb 18-2 and the single chain antibody of the present disclosure have been shown to be different. Furthermore, since the mechanism of action of the single chain antibody of the present disclosure is based on steric inhibition, this result is surprising and unexpected. Therefore, the present disclosure clearly shows unexpected functional differences between the single chain antibody of the present disclosure and mAb 18-2. Therefore, the prior art composition does not perform the same function as the claimed composition. As discussed above.

The Li reference is applicants' own work

As discussed in a previous response to the office action submitted on August 9, 2006, the Li article is the applicants' own work, and the individuals listed on the present application are the sole inventors. As such, Applicants respectfully submit that Li is not proper in the present rejection, even as an auxiliary reference. MPEP Section 715.01(c) states that "Unless it is a statutory bar, a rejection based on a publication may be overcome by a showing that it was published wither by applicant himself/herself or on his/her behalf". Furthermore, case law supports the general proposition that an applicant's own work cannot be used against the

applicant. For example, in In re Facius (408 F.2d 1396, 1406 (CCPA 1969)) the court stated "[C]ertainly one's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar."

Therefore, applicants respectfully suggest that Li is not properly used in the 102(b) rejection as set forth by the Examiner in the current office action.

Conclusion

Considering the foregoing, applicants respectfully suggest Carter could not have taught or suggested "A composition comprising a DNA repair modulator that specifically binds to the sequence KKKYIEIRKEAREAANGDSDGPSYM (SEQ. ID NO.:16), or a portion thereof, and inhibits non-homologous end joining" as stated in claim 1 (and dependent claims 2 and 4) or "A single chain antibody that specifically binds to DNA-PKcs in a region outside of the catalytic domain, wherein the single chain antibody includes complementarity determining regions FTTYDIN (SEQ. ID NO.:18), WIYPGSGNNKYNEKFKG (SEQ. ID NO.:19), GPLNMTGFDY (SEQ. ID NO.:20), KASQDINSYLS (SEQ. ID NO.:21), RANRLVD (SEQ. ID NO.:22), and LQYDELPLT (SEQ. ID NO.:23), in an immunoglobin framework" as stated in claim 5. Applicants respectfully request the Examiner withdraw the rejection.

Rejections Under 35 USC 103(a): Carter in view of Bejcek and Schwarze

The Examiner rejected claims 1, 2, 4, 5 32 and 34-37 under 35 USC 103(a) as being unpatentable over Carter (as applied to claims 1, 2, 4 and 5 above) in view of Bejcek et al. (Cancer Research, 1995, 55:2346-2351) (hereinafter Bejcek) and Schwarze et al. (Science 9-3-99, 285:1569-1572) (hereinafter Schwarze). The Examiner cited Carter for the propositions above and noted that Carter did not teach a single chain antibody comprising a protein transduction domain wherein the single chain antibody inhibits DNA repair by binding to a repair polypeptide and includes CDR regions defined in SEQ ID NOS: 18-23 in an immunoglobulin framework (claim 32) where in the DNA repair polypeptide comprises DNA-PKcs (claim 34), wherein the single chain antibody binds to a region including SEQ ID NO: 16 or a portion thereof (claims 35-36) and inhibits non-homologous end joining. The Examiner cites Bejcek and Schwarze for contributing the teachings omitted by Carter.

Specifically, the Examiner cited Bejcek for the proposition that single chain antibodies can be constructed from monoclonal antibodies and that single chain antibodies overcome several problems associated with intact mAbs. The Examiner cited Schwarze for the proposition that proteins could be delivered into cells by adding a protein transduction domain. The arguments presented above with regard to the 102(b) rejection are hereby incorporated by reference.

As discussed above, Carter does not teach or suggest a single chain antibody that inhibits non-homologous end joining (see discussion above). In addition, as discussed above, if such a single chain antibody was produced there can be no guarantee that such a single chain antibody would share the binding or functional characteristics of the parental mAb. The Bejcek reference clearly states this fact and demonstrates that not all mAbs are capable of generating corresponding single chain antibodies. The failure rate of converting mAbs into corresponding single chain antibodies was greater than 33% in the experiments reported by Bejcek for the CD19 antigen. Furthermore, the applicants have discussed the Examiner's logic in implying characteristics to mAb 18-2 from the characteristics of the single chain antibody of the present disclosure.

Bejcek and Schwarze do not teach or suggest the shortcomings of Carter as pointed out and discussed above. Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in producing a single chain antibody that bound a DNA repair polypeptide (claim 32), wherein the DNA repair polypeptide comprises DNA-PKcs (claim 34) wherein the single chain antibody binds to a region including SEQ ID NO: 16 or a portion thereof (claims 35-36) and inhibits non-homologous end joining.

Therefore, applicants respectfully suggest that the Examiner remove the 103(a) rejection.

Rejections Under 35 USC 103(a): Carter in view of Kelley and Schwarze

The Examiner rejected claims 1, 2, 4, 5, 32 and 34-39 under 35 USC 103(a) as being unpatentable over Carter in view of Bejcek and Schwarze (as applied to claims 1, 2, 4, 5, 32 and 34-37) in further view of Kelley et al. (US Patent No. 6,252,048) (hereinafter Kelley) or Jang et al. (Molecular Breeding, 2002, 9:81-91) (hereinafter Jang).

The rejection over Carter in view of Bejcek and Schwarze is discussed above. The Examiner stated the Kelley and Jang references disclosed the use of nuclear localization signals and chloroplast localization signals to improve nuclear localization and protein expression, respectively. The arguments presented above with regard to the 102(b) and 103(a) rejections are hereby incorporated by reference.

As discussed above, Carter does not teach or suggest a single chain antibody that inhibits non-homologous end joining (see discussion above). In addition, as discussed above, if such a single chain antibody was produced there can be no guarantee that such a single chain antibody would share the binding or functional characteristics of the parental mAb. The Bejcek reference clearly states this fact and demonstrates that not all mAbs are capable of generating corresponding single chain antibodies. The failure rate of converting mAbs into corresponding single chain antibodies was greater than 33% in the experiments reported by Bejcek for the CD19 antigen. Furthermore, the applicants have discussed the Examiner's logic in implying characteristics to mAb 18-2 from the characteristics of the single chain antibody of the present disclosure.

Kelley and Jang do not teach or suggest the shortcomings of Carter as pointed out and discussed above. Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in producing a single chain antibody that bound a DNA repair polypeptide (claim 32), wherein the DNA repair polypeptide comprises DNA-PKcs (claim 34), wherein the single chain antibody binds to a region including SEQ ID NO: 16 or a portion thereof (claims 35-37) and inhibits non-homologous end joining and wherein the single chain antibody comprises a protein transduction domain and an organelle localization signal (claim 38) or where the organelle localization signal is a nuclear localization signal or a chloroplast localization signal (claim 39).

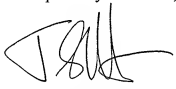
Therefore, applicants respectfully suggest that the Examiner remove the 103(a) rejection.

Conclusion

The above identified applicants respectfully request the Commissioner of Patents consider the enclosed remarks and enter the following submission into the record, in response to

the Examiner's Office Action dated May 17, 2007. Reconsideration in light of this submission is respectfully requested and Applicants respectfully request the application be processed for allowance. If the Examiner requires additional action that may benefit from a telephone call, Applicant invites a call to its attorney of record, T. Gregory Peterson (Reg. No. 45,587) at 205-521-8084. E-mail correspondence and transactions to gpeterson@bradleyarant.com are authorized and encouraged.

Respectfully Submitted,



T. Gregory Peterson
Attorney for the Applicant
Reg. No. 45,587

OF COUNSEL
Bradley Arant Rose & White LLP
1819 Fifth Avenue North
Birmingham, Al 35203-2104
(205) 521-8084